

Q2 proteins, when used at a concentration of at least about 10 µg per 6.5-7.3 mg of bovine tendon collagen in a rat subcutaneous assay, induces a bone score of from about 1.0 to about 3.5, using a bone grading scale set forth in Table 8 (Example 10), and induces a cartilage score of at least about 1.2, using a cartilage grading scale set forth in Table 9 (Example 10). A rat subcutaneous assay suitable for determining bone and cartilage scores according to this aspect, and the grading scales of Tables 8 and 9 are described in detail in the Examples Section.--

IN THE CLAIMS:

Please cancel Claims 14 and 15, without prejudice to or disclaimer of the subject matter therein.

Please amend Claims 1-11, 19, 24-26, 31, 33, 37 and 38, without prejudice to or disclaimer of the subject matter therein. For the Examiner's convenience, Claims 12, 13, 16-18, 20-23, 27-30, 32 and 34-36 are reiterated below without amendment.

Please add new Claims 39-43 as set forth below.

- Q3
1. (Once Amended) A product for repair of cartilage lesions, comprising:
 - a. a cartilage repair matrix suitable for conforming to a defect in cartilage; and
 - b. a cartilage-inducing composition contained on or within said matrix comprising a mixture of proteins comprising: transforming growth factor β1 (TGFβ1), bone morphogenetic protein (BMP)-2, BMP-3, and BMP-7;
wherein the quantity of said TGFβ1 in said mixture is greater than 1% of total proteins in said mixture;
wherein the quantity of said BMP-2 in said mixture is from about 0.01% to about 10% of total proteins in said mixture;
wherein the quantity of said BMP-3 in said mixture is from about 0.1% to about 15% of total proteins in said mixture; and,
wherein the quantity of said BMP-7 in said mixture is from about 0.01% to about 10% of total proteins in said mixture.

41. (Once Amended) A product for repair of cartilage lesions, comprising:

- a. a cartilage repair matrix; and
- b. a cartilage-inducing composition contained on or within said matrix comprising a mixture of proteins comprising:

(i) a bone-derived osteogenic or chondrogenic formulation containing at least one bone morphogenetic protein (BMP); and,

(ii) a TGF β protein that is exogenous to said formulation of (i);

wherein the ratio of said exogenous TGF β protein to total BMP in said mixture of proteins is greater than about 10:1; and,

wherein said exogenous TGF β protein is present in an amount sufficient to increase cartilage induction by said composition over a level of cartilage induction by said bone-derived osteogenic or chondrogenic protein formulation in the absence of said exogenous TGF β protein.

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3. (Once Amended) A product for repair of cartilage lesions, comprising:

- a. a cartilage repair matrix; and
- b. a cartilage-inducing composition contained on or within said matrix comprising a mixture of proteins comprising:

(i) a TGF β protein; and,

(ii) at least one bone morphogenetic protein (BMP);

wherein the ratio of said TGF β protein to total BMP in said mixture of proteins is greater than about 10:1.

⁸
4. (Once Amended) The product of Claim ⁴2, wherein said mixture of proteins comprises TGF β superfamily proteins consisting of: TGF β 1, bone morphogenetic protein (BMP)-2, BMP-3, and BMP-7, wherein said TGF β superfamily proteins comprise from about 0.5% to about 99.99% of said mixture of proteins.

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5. (Once Amended) The product of any one of Claims ⁸4 or ¹⁵42, wherein said TGF β superfamily proteins comprise from about 0.5% to about 25% of said mixture of proteins.

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6. (Once Amended) The product of any one of Claims ⁸4 or ¹⁵42, wherein the quantity of said TGF β 1 in said mixture is from about 0.01% to about 75% of total proteins in said mixture.

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7. (Once Amended) The product of any one of Claims 1, ⁸4 or ¹⁵42, wherein the quantity of said TGFβ1 in said mixture is from about 33% to about 99.99% of total proteins in said mixture.

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8. (Once Amended) The product of any one of Claims 1, ⁸4 or ¹⁵42, wherein said mixture of proteins further comprises at least one bone matrix protein selected from the group consisting of osteocalcin, osteonectin, bone sialoprotein (BSP), lysyloxidase, cathepsin L pre, osteopontin, matrix GLA protein (MGP), biglycan, decorin, proteoglycan-chondroitin sulfate III (PG-CS III), bone acidic glycoprotein (BAG-75), thrombospondin (TSP) and fibronectin; wherein said bone matrix protein comprises from about 20% to about 98% of said mixture of proteins.

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9. (Once Amended) The product of any one of Claims 1, ⁸4 or ¹⁵42, wherein said mixture of proteins further comprises at least one growth factor protein selected from the group consisting of fibroblast growth factor-I (FGF-I), FGF-II, FGF-9, leukocyte inhibitory factor (LIF), insulin, insulin-like growth factor I (IGF-I), IGF-II, platelet-derived growth factor AA (PDGF-AA), PDGF-BB, PDGF-AB, stromal derived factor-2 (SDF-2), pituitary thyroid hormone (PTH), growth hormone, hepatocyte growth factor (HGF), epithelial growth factor (EGF), transforming growth factor-α (TGFα) and hedgehog proteins; wherein said growth factor protein comprises from about 0.01% to about 50% of said mixture of proteins.

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10. (Once Amended) The product of any one of Claims 1, ⁸4 or ¹⁵42, wherein said composition further comprises one or more serum proteins.

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11. (Once Amended) The product of Claim 1, wherein said mixture of proteins further comprises TGFβ2, TGFβ3, BMP-4, BMP-5, BMP-6, CDMP, FGF-I, osteocalcin, osteonectin, BSP, lysyloxidase, cathepsin L pre, albumin, transferrin, Apo A1 LP and Factor XIIIb.

12. (Reiterated) The product of any one of Claims 1, 2 or 3, wherein said mixture of proteins comprises Bone Protein (BP).

13. (Reiterated) The product of any one of Claims 1, 2 or 3, wherein said cartilage-inducing composition is at a concentration of from about 0.5% to about 33% by weight of said product.

16. (Reiterated) The product of Claim 2, wherein said exogenous TGF β protein is TGF β 1.

17. (Reiterated) The product of any one of Claims 1 or 16, wherein the ratio of TGF β 1 to all other proteins in said mixture of proteins is at least about 1:10.

18. (Reiterated) The product of any one of Claims 1 or 16, wherein the ratio of TGF β 1 to all other proteins in said mixture of proteins is at least about 10:1.

19. (Once Amended) The product of any one of Claims ⁴/₂ or ¹⁹/₃, wherein the ratio of said TGF β protein to total BMP in said mixture of proteins is greater than about 100:1.

20. (Reiterated) The product of Claim 3, wherein said TGF β protein is TGF β 1.

21. (Reiterated) The product of Claim 3, wherein said BMP protein is selected from the group consisting of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9 and CDMP.

22. (Reiterated) The product of any one of Claims 1, 2 or 3, wherein said cartilage repair matrix is bioresorbable.

23. (Reiterated) The product of Claims 1, 2 or 3, wherein said cartilage repair matrix comprises collagen from bovine tendon.

24. (Once Amended) A method for repair of cartilage lesions, comprising implanting and fixing into a cartilage lesion a product comprising:

a. a cartilage repair matrix suitable for conforming to a defect in cartilage; and

b. a cartilage-inducing composition contained on or within said matrix comprising a mixture of proteins comprising: transforming growth factor β 1 (TGF β 1), bone morphogenetic protein (BMP)-2, BMP-3, and BMP-7;

wherein the quantity of said TGF β 1 in said mixture is greater than 1% of total proteins in said mixture;

wherein the quantity of said BMP-2 in said mixture is from about 0.01% to about 10% of total proteins in said mixture;

wherein the quantity of said BMP-3 in said mixture is from about 0.1% to about 15% of total proteins in said mixture; and,

wherein the quantity of said BMP-7 in said mixture is from about 0.01% to about 10% of total proteins in said mixture;

whereby implanting and fixing said product into said cartilage lesion enhances repair of said defect in cartilage as compared to in the absence of said product.

27
25. (Once Amended) A method for repair of cartilage lesions, comprising implanting and fixing into a cartilage lesion a product comprising:

- a. a cartilage repair matrix; and,
- b. a cartilage-inducing composition contained on or within said matrix comprising a mixture of proteins comprising:

- (i) a bone-derived osteogenic or chondrogenic formulation of proteins containing at least one bone morphogenetic protein (BMP); and,

- (ii) a TGF β protein that is exogenous to said formulation of (i);
wherein the ratio of said exogenous TGF β protein to total BMP in said mixture of proteins is greater than about 10:1; and,

wherein said exogenous TGF β protein is present in an amount sufficient to increase cartilage induction by said composition over a level of cartilage induction by said bone-derived osteogenic or chondrogenic protein formulation in the absence of said exogenous TGF β protein;

whereby implanting and fixing said product into said cartilage lesion enhances repair of said defect in cartilage as compared to in the absence of said product.

31
26. (Once Amended) A method for repair of cartilage lesions, comprising implanting and fixing into a cartilage lesion a product comprising:

- a. a cartilage repair matrix; and,
- b. a cartilage-inducing composition contained on or within said matrix comprising a mixture of proteins comprising:

- (i) a TGF β protein; and,

- (ii) at least one bone morphogenetic protein (BMP);

wherein the ratio of said TGF β protein to total BMP in said mixture of proteins is greater than about 10:1;

5
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whereby implanting and fixing said product into said cartilage lesion enhances repair of said defect in cartilage as compared to in the absence of said product.

27. (Reiterated) The method of Claim 25, wherein said TGF β protein is TGF β 1.

28. (Reiterated) The method of any one of Claims 24 or 27, wherein the ratio of TGF β 1 to all other proteins in said mixture of proteins is at least about 1:10.

29. (Reiterated) The method of any one of Claims 24 or 27, wherein the ratio of TGF β 1 to all other proteins in said mixture of proteins is at least about 10:1.

30. (Reiterated) The method of Claim 26, wherein said TGF β protein is TGF β 1.

37 31. (Once Amended) The method of any one of Claims 25 or 26, wherein the ratio of said TGF β protein to total BMP in said mixture of proteins is greater than about 100:1.

32. (Reiterated) The method of any one of Claims 24, 25 or 26, wherein said cartilage lesion is an articular cartilage lesion.

34 33. (Once Amended) The method of any one of Claims 24, 25 or 26, wherein said cartilage lesion is a meniscal cartilage lesion.

34. (Reiterated) The method of Claim 33, wherein said lesion is a vascular meniscus lesion.

35. (Reiterated) The method of Claim 33, wherein said lesion is an avascular meniscus lesion.

36. (Reiterated) The method of any one of Claims 24, 25 or 26, wherein said lesion is a tear and wherein said matrix is configured as a sheet, wherein said step of implanting comprises inserting said product directly into said tear.

39 37. (Once Amended) A method for repair of segmental cartilage lesions, comprising implanting and fixing into a segmental cartilage lesion:

a. a first product comprising:

(i) a cartilage repair matrix configured as a sheet; and

(ii) a cartilage-inducing composition contained on or within said matrix comprising a mixture of proteins comprising: transforming growth factor β 1 (TGF β 1), bone morphogenetic protein (BMP)-2, BMP-3, and BMP-

7;

wherein the quantity of said TGF β 1 in said mixture is greater than 1% of total proteins in said mixture;

wherein the quantity of said BMP-2 in said mixture is from about 0.01% to about 10% of total proteins in said mixture;

wherein the quantity of said BMP-3 in said mixture is from about 0.1% to about 15% of total proteins in said mixture; and,

wherein the quantity of said BMP-7 in said mixture is from about 0.01% to about 10% of total proteins in said mixture; and,

b. a second product comprising a cartilage repair matrix configured to replace cartilage removed from a segmental lesion;

wherein said second product is implanted into said lesion and wherein said first product is implanted between an edge of said lesion and said second product to provide an interface between said lesion and said second product.

⁴⁰38. (Once Amended) The method of Claim ³⁹37, wherein said second product further comprises a cartilage-inducing composition contained on or within said matrix comprising a mixture of proteins comprising: transforming growth factor β 1 (TGF β 1), bone morphogenetic protein (BMP)-2, BMP-3, and BMP-7;

wherein the quantity of said TGF β 1 in said mixture is greater than 1% of total proteins in said mixture;

wherein the quantity of said BMP-2 in said mixture is from about 0.01% to about 10% of total proteins in said mixture;

wherein the quantity of said BMP-3 in said mixture is from about 0.1% to about 15% of total proteins in said mixture; and,

wherein the quantity of said BMP-7 in said mixture is from about 0.01% to about 10% of total proteins in said mixture.

⁹39. (Added) The product of Claim ⁴2, wherein said bone-derived osteogenic or chondrogenic formulation comprises TGF β 1, TGF β 2, TGF β 3, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, CDMP, FGF-I, osteocalcin, osteonectin, BSP, lysyloxidase, cathepsin L pre, albumin, transferrin, Apo A1 LP and Factor XIIIb.

See B3

40. (Added) The product of Claim 3, wherein said mixture of proteins comprises TGF β 1, TGF β 2, TGF β 3, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, CDMP, FGF-I, osteocalcin, osteonectin, BSP, lysyloxidase, cathepsin L pre, albumin, transferrin, Apo A1 LP and Factor XIIIb.

21. (Added) The product of Claim 1, wherein the quantity of said TGF β 1 in said mixture is at least about 10% of total proteins in said mixture.

15 42. (Added) The product of Claim 10, wherein said mixture of proteins comprises TGF β superfamily proteins consisting of: TGF β 1, bone morphogenetic protein (BMP)-2, BMP-3, and BMP-7, wherein said TGF β superfamily proteins comprise from about 0.5% to about 99.99% of said mixture of proteins.

23 43. (Added) A product for repair of cartilage lesions, comprising:

a. a cartilage repair matrix suitable for conforming to a defect in cartilage; and

b. a cartilage-inducing composition contained on or within said matrix comprising a mixture of proteins comprising: transforming growth factor β 1 (TGF β 1), bone morphogenetic protein (BMP)-2, BMP-3, and BMP-7;

wherein the quantity of said TGF β 1 in said mixture is greater than 1% of total proteins in said mixture;

wherein the quantity of said BMP-2 in said mixture is from about 0.01% to about 10% of total proteins in said mixture;

wherein the quantity of said BMP-3 in said mixture is at least about 0.38% of total proteins in said mixture; and,

wherein the quantity of said BMP-7 in said mixture is from about 0.01% to about 10% of total proteins in said mixture.